Paper No. 35

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte ALFONS CARCASONA, WOLF GRIMMINGER,
PENTTI HIETALA, KLAUS WITTHOHN and HELGA ZAESKE

Appeal No. 2001-1259
Application 08/337,671

ON BRIEF

Before WINTERS, SCHEINER, and MILLS Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 18-20, which are the claims pending in this application.

Claims 18 and 20 are representative of the claims on appeal and read as follows.

18. Diacetylrhein, which is substantially free of aloe-emodin components, obtained by:

a) admixing a mixture of rhein-9-anthrone-8-glucoside and aloe-emodin-9-anthrone-8-glucoside with an aqueous solution having a pH of 6.5 to 7.5 and with a polar organic solvent which is incompletely miscible with water,

b) subjecting the resulting mixture to liquid-liquid partitioning to form a light organic phase containing said aloe-emodin-9-anthrone-8-glucoside and a heavy aqueous phase containing said rhein-9-anthrone-8-glucoside,

c) separating said aqueous phase from said organic phase,

d) oxidizing the rhein-9-anthrone-8-glucoside contained in said aqueous phase to rhein-8-glucoside,

e) treating said rhein-8-glucoside with an acid to remove the glucose in the 8-position and form substantially pure rhein,

f) acetylating said rhein to form substantially pure diacetylrhein containing less than 20 ppm aloe-emodin components, and

g) recovering said substantially pure diacetylrhein.

20. An anti-arthritic pharmaceutical composition comprising an arti-arthritically effective dose of substantially pure diacetylrhein containing less than 20 ppm aloe-emodin components and a pharmaceutically acceptable inert carrier.

The references relied upon by the examiner are:

Friedmann	4,244,968	Jan. 13, 1981

Grounds of Rejection

Claims 18-19 stand rejected under 35 U.S.C. § 102 or in the alternative under 35 U.S.C. § 103(a) as obvious over Friedmann or Merck Index.

Claim 20 stands rejected under 35 U.S.C. § 103(a) as obvious over either Friedmann or Merck Index.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, to the applied prior art references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the above-noted rejection, we make reference to the Examiner's Answer for the examiner's complete reasoning in support of the rejection, and to the appellants' Brief and Reply Brief for the appellants' arguments thereagainst. We have considered this appeal along with related appeal No. 2001-1947, Serial No. 08/333,202. As a consequence of our review, we make the determinations which follow.

35 U.S.C. § 102 and 103

Claim 20 stands rejected under 35 U.S.C. § 103(a) as obvious over either Friedmann or Merck Index.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1993).

It is the examiner's position that (Answer, page 3):

> The claims are product-by-process claims drawn to the compound diacetylrhein. . . . Friedmann teaches the compound diacetylrhein and its use for the treatment of arthritis. . . . The compound taught by Friedmann would inherently be substantially pure, essentially free from aloe-emodin derivatives.

According to the examiner, "[t]here is no apparent difference in the compounds. . . . To the extent that the purity of the compound of the reference and that of the claims differ, the claims are rejected under 35 U.S.C. § 103 (a)." Id. Merck also

With respect to claim 20, the examiner finds that the composition of claim 20 reads on a water solution of the acetylrhein compound citing Friedmann, column 8, lines 35 and 54 and Merck Index Abstract 8072, page 1179. Answer, page 4.

Assuming, arguendo, that the examiner has presented a prima facie case of obviousness, appellants provide argument, and rebuttal evidence in the form of a Declaration under 37 CFR § 1.132 of Dr. Grimminger.

Appellants first argue that "[n]owhere does Friedmann disclose the purity of his [purified diacetylrhein]." Brief, page 4. Appellants further argue that, contrary to the examiner's assertion, Friedmann's pharmaceutical use of diacetylrhein cannot be equated to less than 20 ppm aloe-emodin content. Appellants argue that evidence of record[1] shows that Proter, Friedmann's assignee, produces a diacetylrhein having a much higher aloe-emodin content. Id.

In particular, appellants have made of record Analysis Certificates "which permit a direct comparison of the product according to the state-of-the-art with the product of the method of the now claimed invention." Paper No. 15, page 5. The comparison contains the results of the analysis of three batches of diacetylrhein prepared by the firm of Proter, (U.S. Patent No 4,244,968 (Friedmann) and DE 27 11 493). The appellants tested the Proter product and found an aloe-emodin content of 1400 ppm,

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2000 ppm and 900 ppm, respectively. Paper No. 15, page 6. In contrast, appellants provided multiple batch analysis of diacetylrhein prepared by the claimed process which indicated an aloe-emodin content of 2 ppm. Id. Thus, appellants argue there is no teaching in Friedmann that less than 20 ppm aloe-emodin content of diacetylrhein is desirable or attainable. Brief, page 5.

With respect to the Merck reference cited by the examiner, appellants argue that "Friedmann begins preparation of his product using Sennosides A and B as set forth in the Merck Index. Friedmann then goes on to state that the "crude" rhein is collected. Thus, Friedmann himself certainly leads the skilled artisan to the conclusion that one would have to purify the product prepared according to the Merck Index." Brief, page 7.

In the Declaration under 37 CFR § 1.132 , Dr. Grimminger states:

> To appreciate the significance of the now claimed invention, one must be familiar with the state-of-the-art preparations commercially available and the techniques used for industrial preparations. At present, there are two principal methods of preparing diacerein on an industrial scale. . . .

These two methods are 1) oxidation of acetyl aloin and 2) acetylation of rhein. Declaration, page 3. Dr. Grimminger states that, "[t]ests have shown that diacerein, which according to reference 4 in the literature, is prepared from acetylated

recrystallization which is required for medicinal products, the residue of total aloe emodin still exceeds 1000 ppm." Declaration, pages 3-4.

As to differing properties associated with the claimed diacetylrhein, Dr. Grimminger indicates that "[g]enotoxicity tests performed parallel to the clinical development provide positive findings in the mouse lymphoma test and in the CHO test with a substance containing in excess of 1000 ppm triacetyl aloe emodin. Repeated investigations with a purified substance (66 ppm total aloe emodin residue) and with high-purity rhein provided negative results." Declaration, page 2.

The examiner responds to the Grimminger Declaration evidence, arguing, "based on the assumption that applicant is right and the compound taught by Friedmann was made by Proter, the examiner points to the article by Neuman, in Drugs of the Future wherein, it is stated that pharmatoxicologic tests using DAR[2] produced by Proter showed an absence of side effects, mutagenic properties and of peri and post-natal toxicity. (Neumann [sic], page 446)." Answer, page 5.

The examiner further argues that Dr. Grimminger states that the "second method referred to by Neuman in Drugs of the Future[3] yields a DAR having greater than 1000 ppm aloe-emodin content..." Answer, pages 5-6. The examiner finds that "applicant

has made no reference to the other process disclosed by the article [Neuman]." Answer, page 6. We disagree.

The first (other) process of synthesis of acetylrhein mentioned in Neuman is that of oxidation of acetylbarbaloin. Dr. Grimminger has indicated in paragraph 6 of his Declaration that reference 4[4] attached to the Declaration describes a process of oxidation of aloin resulting in a diacetylrhein which still has a total aloe emodin content of approximately 3500 ppm at a concentration of 95%. Following the increase in concentration to >98% by means of recrystallization which is required for medicinal products, the residue of total aloe emodin still exceeds 1000 ppm. We find this reference and process discussed in the Grimminger Declaration to be representative of the method of preparing diacetylrhein by oxidation of barbaloin[5] mentioned in Neuman.

The examiner argues that the opinion of Dr. Grimminger in the Declaration is afforded less weight than objective data which can be independently evaluated. Answer, page 7.

The Declaration of Grimminger must be properly weighed. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983)("evidence

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[4] "Experiments on the Constitution of the Aloins Part I," by Robert Robinson and

rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness."). The examiner finds the statements presented in the Declaration of Grimminger to be merely opinion. Although factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue. While an opinion as to a legal conclusion is not entitled to any weight, the underlying basis for the opinion may be persuasive. In re Chilowsky, 306 F.2d 908, 134 USPQ 515 (CCPA 1962). We find, however, that Dr. Grimminger's statements are supported by at least some factual basis and evidence of the state of the art.

In addition, although an affiant's or declarant's opinion on the ultimate legal issue is not evidence in the case, "some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him." In re Lindell, 385 F.2d 453, 456, 155 USPQ 521, 524 (CCPA 1967). The weight attached to evidence of secondary considerations depends upon its relevance to the issue of obviousness and the amount and nature of the evidence.

We are persuaded by the argument and evidence presented by appellants. In view of appellants' evidence, in our view both Friedmann and Merck fail to disclose

Hoeksema.[6] We find appellants have provided sufficient evidence to support the position that the prior art products and methods of making diacetylrhein are not, and do not enable a method of making, a compound having the claimed purity. This evidence has been insufficiently rebutted by the examiner.

In our view, and consistent with legal precedent, a compound in purer or modified form may, if unobvious in that form, be patentable over the same compound as it existed in the prior art but the claims thereto must be limited so as to exclude from the scope thereof, the compound as it existed in nature. In re Kebrich, 201 F.2d 951, 954, 96 USPQ 411, 413 (CCPA 1953). Compare In re Williams, 171 F.2d 319, 320, 80 USPQ 150, 152 (CCPA 1948). We find appellants have sufficiently limited the scope of their purer form of diacetylrhein to a diacetylrhein containing less than 20 ppm aloe-emodin components.

It has also been held that a compound/substance extracted from its parent material even in purer form is patentable only if it possesses a utility not possessed by the parent material and not evident from the art. Ex parte Reed, 135 USPQ 34 (Bd. App. 1962). In our view, appellants have established that the state of the art is that prior art methods of preparing diacetylrhein, and therefore prior art products produced

from these methods, have not provided a diacetylrhein product with less than 20 ppm of aloe-emodin. Appellants also provide evidence that the claimed product differs from prior art products in its mutagenicity properties.

After evidence or argument is submitted by the applicant in response to an obviousness rejection, "patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument." In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); see In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787 (Fed. Cir. 1984) ("All evidence on the question of obviousness must be considered, both that supporting and that rebutting the prima facie case."). On balance, we believe that the totality of the evidence presented by the examiner and appellants weighs in favor of finding the claimed invention nonobvious in view of the cited references. The rejection of the claims for anticipation, or in the alternative for obviousness of the claimed invention, is reversed.

Upon return of the application to the examiner, it is recommended that the examiner review Serial No. 08/333,202 (Appeal No. 2001-1947) to determine if any double patenting issues exist, in particular between claim 20 of the pending application and claim 22 of Serial No. 08/333,202.

CONCLUSION

The rejection of claims 18-19 under 35 U.S.C. § 102 or in the alternative under 35 U.S.C. § 103(a) as obvious over Friedmann or Merck Index is reversed. The rejection of claim 20 under 35 U.S.C. § 103(a) as obvious over Friedmann or Merck Index is reversed. The application should be further reviewed for possible double patenting issues.

REVERSED

SHERMAN D. WINTERS)
Administrative Patent Judge)
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) BOARD OF PATENT
TONI R. SCHEINER)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
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